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To: Harold_Varmus@nih.gov
From: Barbara Wold <woldb@cco.caltech.edu>
Subject: Re: review/Collins
Cc: WOLDB@starbase1.caltech.edu

Dear Harold,

No, I will not make it to CSH, and that is a regret, but I absolutely had to have two weeks in town to meet teaching and thesis finishing demands. Hunkapiller was here visiting yesterday, and I have not seen such a stir over matters genomic since Lee proposed a 200 person effort here many years ago. Below are some immediate thoughts. Not all, and not well ordered - but you know the subject inside and out - so for what they may be worth as a starting point:

First, the current idea that the public sector goal is building sustainable sequencing capacity and improving it further for longterm use past the reference human genome is useful. (Disclaimer - this may be a matter of getting too enchanted with my own focus in this process, so discount accordingly). Conservative quality goals with respect to error and ambition on contiguity (and measuring and facing the deferred costs of contiguity sooner versus later) are important in the public framework, but vague and clearly very flexible in the private effort. On both sides this seems a good match of purposes and resources (there is a contiguity subtlety that I have been thinking about in which different centers in the public effort might be encouraged to take somewhat different attacks on contiguity, within bounds so that we see how much the cost is but allow for the possibility that we will get lots better at it later in the process and some deferral may be smart - but that is minor for the larger issue at hand).

So, taking one extreme outcome: If the private effort delivers the max of what is promised, and we can evaluate quality in the significant size zones of overlap between NIH sequence and theirs when they are a year into their project, then it may be that NIH/DOE can focus more on the closing that they do not apparently intend and on moving toward mouse. Why do I see this as such a good outcome? Not because I work on mouse, though that has not escaped me. It is the importance of mouse to the human project for "interpretation" (beginning with gene finding but extending immediately to regulation problems) seems a really important idea, and one that may not be adequately appreciated. In this regard the testimonials from Bob Horvitz and others in worm community about the value of the second (related) worm genome for using the first is a lovely real life example (I thought I would use it at Arlie).

Taking the other extreme outcome: What if the private effort turns out to have major defficiencies or the company pulls the plug halfway through, or the accessibility of the data is much more restricted than advertised? Then the public effort clearly will be the effort of record and needs to proceed thinking that this will be the cse. In this vein, I think we might also need to talk very frankly about the challenge of managing risk/benefit in this enterprize. That includes owning up to the fact that we collectively do not have experience on this scale and the track record is mixed at best. And whose fault is that, if anyone's? Perhaps it should be viewed as the nature of the beast. Less blue sky. Really expect shutdowns of some centers and replacement by others. Evolution in its most brutal sense on a grand and visible scale. This also makes more sense if high quality, increasingly economical capacity is the goal rather than with the reference human sequence as the goal.

Also I detect the subtext that NIH or GOVERNMENT is under indictment by the very appearance of this private effort. This may be where both long term goals and risk benefit issues need to be emphasized. It seems to me that the private and public efforts are quite different beasts in terms of risk/benefit. Also on the NIH side, I see the larger community not taking proper responsibility for the peer review in both technology development and in the big sequencing. That is, I hear "THE NIH CENTRAL COMMITTEE" made this or that poorly chosen decision/ set this or that poorly considered standard (the 1 in 10,000 error rate based on SNP discovery as a goal lends some fuel to the fire, and that might be worth batting around in a conversation) If the private effort falls short, they can respond in a variety of ways (including instant pulling of the plug or substantial shift in goals and quality that the public effort cannot do).

Though I will not be at CSH, if you want to talk by phone someday, just let me know. BJW

Barbara Wold

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